Can Serum Fibrinogen Predict ARDS?

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ABSTRACT: Acute respiratory distress syndrome (ARDS) has a worldwide mortality of 10% to 30% with severe pneumonia being the primary cause. Diagnosis relies on clinical criteria which may lead to under-recognition and delayed evidence-based interventions. In previous studies, plasma fibrinogen was associated with progression to ARDS among patients with severe pneumonia. This is a prospective cohort study wherein we hypothesized that levels of plasma fibrinogen and change in levels of fibrinogen can predict development of ARDS among a cohort of patients with severe pneumonia based on the Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) consensus criteria. After acquiring consent, plasma fibrinogen levels were extracted upon enrollment and after 48 hours. These extraction times were arbitrarily chosen to determine whether levels rise or decline in relation to the course of disease. A total of 47 patients were prospectively followed within 7 days of enrollment, then divided into 2 groups, which included those who developed ARDS (n = 12, 25%) and those who did not (n = 35, 75%). Fibrinogen levels at baseline had sensitivity and specificity of 41.7% and 57.1%, respectively (*P* = .932) with an area under the curve (AUC) of 0.492; levels after 48 hours had sensitivity and specificity of 55.6% and 65.6%, respectively (*P* = .729) with an AUC of 0.538; and delta fibrinogen levels had sensitivity and specificity of 55.6% and 62.5%, respectively (*P* = 0.581) with an AUC of 0.561. Based on this study, plasma fibrinogen is an unreliable biomarker for predicting ARDS development in patients with severe pneumonia. In setting up this study, we experienced limitations which we had to accept but realizations of these led to the discovery of potential research areas. To our knowledge, this is the first Philippine study attempting to discover a biomarker for ARDS progression. It is recommended that further investigation on local incidence and other biomarkers for ARDS should be done.

KEYWORDS: ARDS, biomarkers, fibrinogen, severe pneumonia

Introduction

Acute respiratory distress syndrome remains to be a worldwide problem with an annual intensive care unit (ICU) admission point prevalence of 10.4%.[1-4] Despite advancements in acute respiratory distress syndrome (ARDS) management, it remains a major cause of death among ICU patients with a mortality rate of 30% to 50%.[5] Currently, there is no standardized diagnostic biomarker that is validated for predicting progression to ARDS; instead, clinicians rely on the Berlin Criteria for diagnosis.[1]

Such discrepancies may be due to the fact that the Berlin Criteria is nonspecific for ARDS. It may present with symptoms not necessarily covered by the Berlin criteria, as certain cases may be indolent and slow-progressing.[3] The criteria also fail to take into account the clinical and biochemical heterogeneity of ARDS cases, which adds credence to the assertion that the condition is currently being underdiagnosed.[5,6]

The pathophysiologic basis of ARDS revolves around the mechanisms of acute lung injury.[7] Activation of the coagulation cascade has been identified among patients with severe sepsis due to the pro-inflammatory nature of the condition. This induces platelet activation and inhibition of fibrinolysis, resulting in an increase in fibrin production, which is predicated by increased fibrinogen levels.[8] Several studies have focused on these mechanisms in pursuit of ARDS-specific biomolecular markers that can aid in the early diagnosis of ARDS[7,9] but these tests are not readily available in the Philippines at present.

Luo et al[4] performed a retrospective study on patients with severe pneumonia, diagnosed using the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) guidelines who developed ARDS. They identified that patients with ARDS had both serum fibrinogen levels and positive end-expiratory pressure (PEEP) > 6.5 as independent predictors for mortality. This study was the basis for our decision to limit our inclusion criteria using the same cohort.

Granting the difficulties of diagnosing ARDS using solely clinical criteria,[10-13] a biomarker can help clinicians deliver early and appropriate interventions, especially for patients who do not fall under the Berlin Criteria (ie, pseudo-ARDS).[12,14] Most of the sophisticated diagnostic markers are exclusive to high-income nations and are inaccessible to low- and middle-income countries such as the Philippines. There is a need to discover biomarkers that are readily available to clinicians to facilitate the identification and timely management of ARDS, especially in areas where it is still under-recognized.[4,7,9,14-18] Therefore, we designed this study aimed to investigate the clinical utility of plasma fibrinogen in predicting progression to

ARDS among patients with severe pneumonia. We hypothesized that fibrinogen levels are associated with development of ARDS and will increase as pneumonia worsens and transitions to ARDS.

Methodology

This was an Institutional Review Board (IRB) approved, prospective cohort study done at a university-affiliated hospital in the Philippines. The study was conducted over a 7-month period from July 2018 to February 2019. IRB number: GCS MED2018-068.

We calculated a sample size of 44 patients assuming a power of 80%, a confidence interval of 95%, a 5% margin of error, and a 5% between-group difference. This calculation was also based on a previously reported Asia period prevalence[2] plus local registry data.

Participants include adult patients (≥18 years of age) admitted from the emergency department, ICU, or wards, who were diagnosed with severe pneumonia based on the consensus criteria of the IDSA and ATS. These include fulfilling either one major criterion between acute respiratory failure requiring invasive mechanical ventilation or septic shock with need for vasopressors, or at least 3 minor criteria (respiratory rate ≥30 breaths per minute, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (Pao_2/Fio_2) ≤250, blood urea nitrogen ≥20 mg/dL, white blood cell count <0.4×10^9/L, platelet count <100×10^9/L, body temperature <36°C, multilobar infiltrates, confusion/disorientation, and hypotension requiring aggressive fluid resuscitation).[19] Patients with overt heart failure, underlying respiratory comorbidities (chronic obstructive pulmonary disease, bronchiectasis), liver and hematologic disorders, or malignancy, as well as pregnant patients, patients with ARDS on enrollment, and patients with advance directives, were excluded from this study.

Participants were followed prospectively over 7 days and demographic, clinical, and biochemical parameters were collected from the medical records using a data collection form. All participants were given control numbers to maintain anonymity. Written informed consent was obtained. A severity of illness score using the APACHE II tool was determined. Plasma fibrinogen determination using Clauss assay was done with an automated blood coagulation analyzer (Sysmex) CA-500 at 2 points on all patients, initially within 24 hours of diagnosis as baseline and then after 48 hours. The decision behind the 48th hour redetermination was arbitrary due to the paucity of literature exploring the relationship of fibrinogen levels and the progression of pneumonia to ARDS.

Clinical course of participants was then followed until the seventh day of observation and clinical status was recorded as (1) improved, (2) status quo, (3) developed ARDS, or (4) expired. Participants were considered improved if they met the following: extubated and transferred out of the ICU with no escalation of initial antibiotics. Status quo is when participants maintained the same clinical status as the time of enrollment.
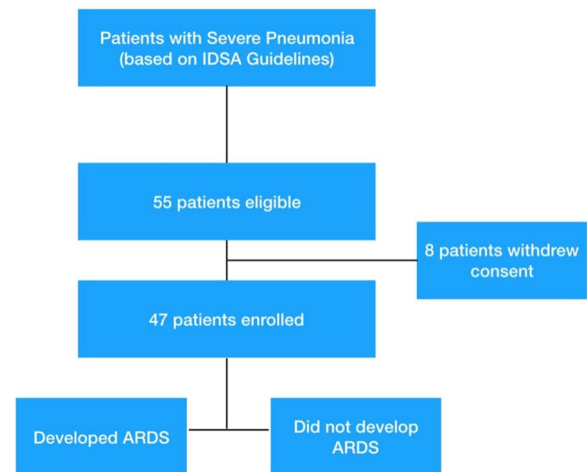
Figure 1. Patient flow. ARDS indicates acute respiratory distress syndrome; IDSA, Infectious Diseases Society of America.

Diagnosis of ARDS within the observation period was made by the attending physician, pulmonologist, or the intensivist on duty based on clinical parameters and the Berlin Criteria.

Analysis

Data are presented in terms of means with standard deviations at a confidence interval of 95%. Participants were divided into 2 outcome groups: (1) patients with severe pneumonia who developed ARDS and (2) patients with severe pneumonia who did not develop ARDS. Chi-square test of independence was used for categorical variables and the independent samples T test was used for continuous variables after a test for normality was performed. We used SPSS 21.0 (Copyright © SPSS Inc. 1989-2007) for all statistical analyses done, using P value of <.05 for detecting statistical difference.

Three plasma fibrinogen measurements were tested: (1) fibrinogen level at baseline (q0h), (2) fibrinogen level after 48 hours (q48h), and (3) percentage change in fibrinogen level (delta fibrinogen) from baseline to 48 hours. Receiver operating characteristic (ROC) curve and area under the curve (AUC) analysis were used to determine fibrinogen's predictive accuracy to determine development of ARDS among patients with severe pneumonia. An AUC of >0.7 to 0.8 is usually deemed as acceptable. However, because the context of this study is medical prediction, we opted to use a cutoff value of >0.9 to affirm predictivity. The ROC cutoff points were identified when the Youden index reached the maximum; sensitivity and specificity were calculated accordingly.

Results

General population

A total of 55 patients with severe pneumonia were initially included in the study; however, 8 patients (14%) withdrew consent. A total of 47 patients (85%) were enrolled and prospectively followed (Figure 1). Most were males with an average age of 61 years (SD: 22.1). Their ideal body weight ranged from 40

Table 1. Patient profile and development of acute respiratory distress syndrome.

PARAMETERS	FREQUENCY / RANGE	PERCENT/ MEAN $\pm$ SD	SP WITHOUT ARDS AFTER 7 D (N = 35)	SP WITH ARDS AFTER 7 D (N = 12)	*P* VALUE
Demographics					
Age, y	19-96	61.4 $\pm$ 22.10	59.5 $\pm$ 23.4	67.0 $\pm$ 17.6	.318[ns]
Gender					
Female	20	42.6	14 (40%)	6 (50%)	
Male	27	57.4	21 (60%)	6 (50%)	
Ideal body weight, kg/m²	40.5-72.0	56.05 $\pm$ 8.01	56.1 $\pm$ 7.8	55.9 $\pm$ 8.9	.941[ns]
Vital signs					
GCS	3-15	9.87 $\pm$ 4.04	9.7 $\pm$ 4.2	10.5 $\pm$ 3.6	.538[ns]
Blood pressure					
Systolic, mm Hg	60-200	117.4 $\pm$ 27.4	117.9 $\pm$ 23.5	116.2 $\pm$ 38.0	.863[ns]
Diastolic, mm Hg	40-110	72.6 $\pm$ 15.9	73.3 $\pm$ 15.2	70.7 $\pm$ 18.3	.631[ns]
Heart rate (per minute)	30-159	94.7 $\pm$ 27.6	92.7 $\pm$ 30.0	100.6 $\pm$ 18.9	.400[ns]
Respiratory rate (per minute)	0-38	27.6 $\pm$ 6.9	28.0 $\pm$ 5.6	28.9 $\pm$ 5.7	.629[ns]
Temperature, °C	35.3-40.3	37.08 $\pm$ 0.91	37.2 $\pm$ 0.9	36.7 $\pm$ 0.7	.145[ns]
O_2 saturation, %	60-100	88.7 $\pm$ 9.1	88.6 $\pm$ 10.2	88.9 $\pm$ 4.9	.926[ns]
Comorbidities					
Neurological	13	27.7	9 (26%)	4 (33%)	.713[ns]
Cardiovascular	30	63.8	21 (60%)	9 (75%)	.492[ns]
Gastrointestinal	1	2.1	0 (0%)	1 (8%)	.255[ns]
Genitourinary	9	19.1	8 (23%)	1 (8%)	.412[ns]
Endocrine	13	27.7	12 (34%)	1 (8%)	.136[ns]
Others	18	38.3	11 (31%)	7 (58%)	.168[ns]
APACHE II			17.8 $\pm$ 6.4	20.0 $\pm$ 5.1	.295[ns]

Abbreviations: ARDS, acute respiratory distress syndrome; GCS, Glasgow Coma Scale; mm Hg, millimeters of mercury; SP, severe pneumonia.
ns—not significant.

to 72 kg, with an average of 56 kg. Majority have comorbidities that are cardiovascular (64%) in nature. The participants had an average sensorium of Glasgow Coma Scale (GCS) 9, 117/73 mm Hg for blood pressure, 95 beats per minute (bpm) for heart rate, 28 breaths per minute for respiratory rate, 37.1°C for temperature, and 89% for O_2 saturation level (Table 1). The demographic and patient profile variables did not exhibit statistical detectable differences for the observations seen.

Characteristics between subgroups

Of the 47 participants enrolled, 12 patients or 25% were found to have developed ARDS within the observation period. Those who developed ARDS had a mean age of 67.0 $\pm$ 17.6 years and

had a mean ideal body weight of 55.9 $\pm$ 8.9. They also have a mean GCS score of 10.5 $\pm$ 3.6, had systolic blood pressures of 116.2 $\pm$ 38.0 with diastolic pressures of 70.7 $\pm$ 18.3. Their mean heart rate was at 100.6 $\pm$ 18.9 with a mean oxygen saturation of 88.9 $\pm$ 4.9. Participants who developed ARDS are mostly those with neurological, cardiovascular, and gastrointestinal comorbidities (Table 1).

Subgroups and laboratory parameters

Participants who developed ARDS within the observational period have a mean APACHE II score of 20.0 $\pm$ 5.1, mean hemoglobin levels of 140.7 $\pm$ 25.5, and mean baseline plasma fibrinogen levels of 492.1 $\pm$ 187.7. Those who developed ARDS

Table 2. Laboratory tests and development of acute respiratory distress syndrome.

PARAMETERS	SP WITHOUT ARDS AFTER 7 D (N = 35)	SP WITH ARDS AFTER 7 D (N = 12)	P VALUE
Hemoglobin, g/L	127.4 ± 22.9	140.7 ± 25.5	.098ns
White cell count, $\times 10^9$/L	15.40 ± 6.88	12.41 ± 9.14	.239ns
Platelet count, $\times 10^9$/L	283.4 ± 133.7	196.8 ± 57.5	.036*
Neutrophils, %	80.1 ± 11.1	77.8 ± 13.1	.570ns
pH	7.337 ± 0.119	7.319 ± 0.121	.660ns
Pao_2	148.3 ± 112.6	118.1 ± 94.2	.409ns
$Paco_2$	55.0 ± 61.6	47.6 ± 18.2	.687ns
HCO_3	22.4 ± 9.3	25.1 ± 10.5	.406ns
O_2 saturation, %	93.6 ± 10.0	93.1 ± 4.7	.875ns
PF ratio	303.1 ± 297.4	152.7 ± 101.9	.204ns
eGFR, mg/dL	57.0 ± 38.0	55.7 ± 37.0	.923ns
Fibrinogen, mg/dL, q0h	473.3 ± 164.5	492.1 ± 187.7	.743ns
Fibrinogen, mg/dL, q48h	513.3 ± 210.0	526.0 ± 196.3	.872ns
% Change in fibrinogen or delta fibrinogen	12.58 ± 34.98	7.98 ± 40.46	.738ns

Abbreviations: ARDS, acute respiratory distress syndrome; eGFR, estimated glomerular filtration rate; g/L, grams per liter; HCO_3, bicarbonate; mg/dL, milligrams per deciliter; Pao_2, partial pressure of oxygen; $Paco_2$, partial pressure of carbon dioxide; PF ratio, Pao_2/Fio_2 ratio; SP, severe pneumonia.
ns—not significant.
*Significant at 5%.

had mean pH levels of 7.319 ± 0.121 with mean Pao_2 levels of 118.1 ± 94.2. They also had mean PF ratios of 152.7 ± 101.9. We observed that only the platelet count exhibited statistical significance related to development of ARDS ($P = .036$, mean of 283.4 ± 133.7 for those who did not develop ARDS versus 196.8 ± 57.5 for those who had ARDS) (Table 2).

Subgroups, ventilation strategy, and treatment outcomes

Most of those with ARDS were intubated and ventilated on volume A/C mode (Table 3) with tidal volume given at 6 to 7 mL/kg (Table 4). In terms of status after 7 days, most improved (n = 19, 40.4%) (Figure 2). Only PEEP was found to exhibit statistically detectable difference with development of ARDS ($P = .020$, 8.5 ± 4.5 for those who developed ARDS versus 6 ± 2.3 for those who did not) (Table 4).

AUROC and fibrinogen levels

Based on Table 5, all 3 variables subjected to ROC curve (Figures 3-5) and AUC analysis were found to be nonsignificant discriminating variables. The AUC was computed to be equal to 0.492 for fibrinogen levels at baseline, 0.538 for levels after 48 hours, and increased to 0.561 for delta fibrinogen. In terms of the primary outcome, fibrinogen levels did not significantly change from the baseline and after 48 hours from the time of diagnosis, making delta fibrinogen a nonspecific and nonsensitive biomarker for predicting progression to ARDS.

Discussion

Based on our results, we were unable to reproduce the findings seen by Luo et al.[4] We observed that baseline fibrinogen, 48-hour fibrinogen levels, and delta fibrinogen were not able to predict progression to ARDS within 7 days using the same cohort of patients with severe pneumonia on enrollment. Various reasons may be able to account for these discrepancies. Luo et al[4] had a larger sample size and a retrospective design, whereas this study was done using a prospective design and had a smaller sample size. Bellani et al[2] reported a worldwide incidence of 10.4% of ICU admissions for ARDS with Asia contributing only a small regional period prevalence of 0.24 cases per ICU beds over 4 weeks. Philippine local data on prevalence of ARDS are unavailable to date. Furthermore, 8 patients from the original enrolled participants withdrew their consent. We also limited our study population to patients with severe pneumonia and did not have a negative control group (ie, patients with ARDS coming from an extra-pulmonary or indirect

Table 3. Treatment strategies and development of acute respiratory distress syndrome.

PARAMETERS	SP WITHOUT ARDS AFTER 7 D (N = 35)	SP WITH ARDS AFTER 7 D (N = 12)	P VALUE
Treatment strategy			.671[ns]
Mechanical ventilation			
Volume A/C	24 (68.5%)	10 (83.3%)	
Pressure A/C	5 (14.2%)	1 (8.3%)	
CPAP PS 10	1 (2.8%)	0 (0%)	
Noninvasive ventilation	1 (2.8%)	0 (0%)	—
High-flow O_2	0 (0%)	1 (8.3%)	—
Low-flow O_2, L/min			
4	1 (2.8%)	0 (0%)	—
6	1 (2.8%)	0 (0%)	—
10	1 (2.8%)	0 (0%)	—
15	1 (2.8%)	0 (0%)	—

Abbreviations: ARDS, acute respiratory distress syndrome; A/C, assist control; CPAP, continuous positive airway pressure; PS, pressure support; SP, severe pneumonia.
ns—not significant.

Table 4. Initial mechanical ventilation setting.

PARAMETER	SP WITHOUT ARDS AFTER 7 D	SP WITH ARDS AFTER 7 D	P VALUE
VTE, mL	391.7 ± 70.8	394.5 ± 65.3	.907[ns]
PEEP, cmH_2O	6.0 ± 2.3	8.5 ± 4.5	.020*
Fio_2	0.56 ± 0.28	0.67 ± 0.28	.266[ns]

Abbreviations: ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure; SP, severe pneumonia; VTE, exhaled tidal volume.
ns—not significant.
*Significant at 5%.

cause). Fibrinogen, also, is a nonspecific inflammatory marker and levels may rise with any inflammatory process. At the time of extraction, numerous factors could lead to instances affecting fibrinogen levels (ie, endotracheal intubation, concomitant sepsis, multiple blood extractions, high catecholamine surge situations). Another possible reason for the discrepancy with our results could be that the 48-hour window to recheck fibrinogen was untimely. The ideal time of redetermination in a cohort of patients with severe pneumonia is still uncertain. With a half-life of 4 days,[8] it could be that the 48-hour redetermination was either premature or late as we still do not know when fibrinogen levels peak.

Both studies showed that the use of higher PEEP exhibited statistically detectable significance and may reflect similarities of ventilation strategies between institutions. It was observed that most of the intubated patients were ventilated using a low tidal volume strategy, most likely indicating a "safe default" approach to prevent ventilator-induced lung injury (VILI) and development of ARDS, which parallels current recommendations[12] (Table 4). Nevertheless, it could have been that the use of higher

PEEP was a consequence of pneumonia transitioning to ARDS or that the higher PEEP-induced VILI which led to ARDS[20,21] (Table 4). It could be that the use of higher PEEP may have induced lung parenchymal inflammation that could trigger fibrinogenesis and thus higher levels of fibrinogen in serum extraction. On the contrary, higher use of PEEP to increase oxygenation could be the consequence of ARDS development among patients with higher fibrinogen levels. The relationship between higher PEEP and fibrinogen can only be described in this study and is hypothesis-generating but cannot be concluded on, as this study was not designed to elaborate an association between the two.

Previous studies[1,11-13,22] have alluded to the possibility of physician ARDS under-recognition. In our study, the diagnosis of ARDS was dependent on the adjudication of the intensivist on duty and/or the attending pulmonologist. Ferguson and colleagues[13] found that ARDS is under-recognized by clinicians due to differences in definitions and perceptions, which may account for the low regional incidence of ARDS. Finally, the clinical heterogeneity of the ARDS population is a
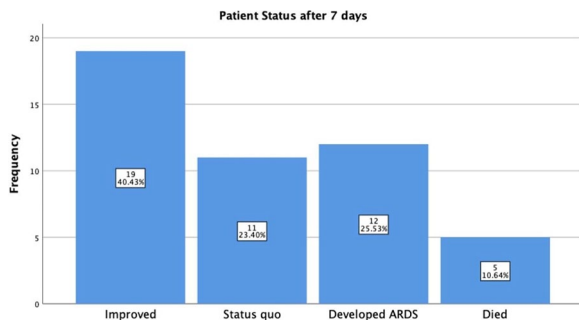
Figure 2. Participant's status after 7 days. ARDS indicates acute respiratory distress syndrome.
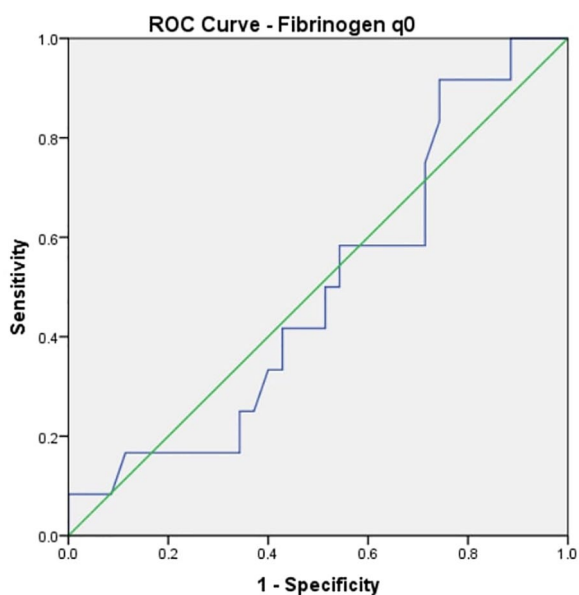
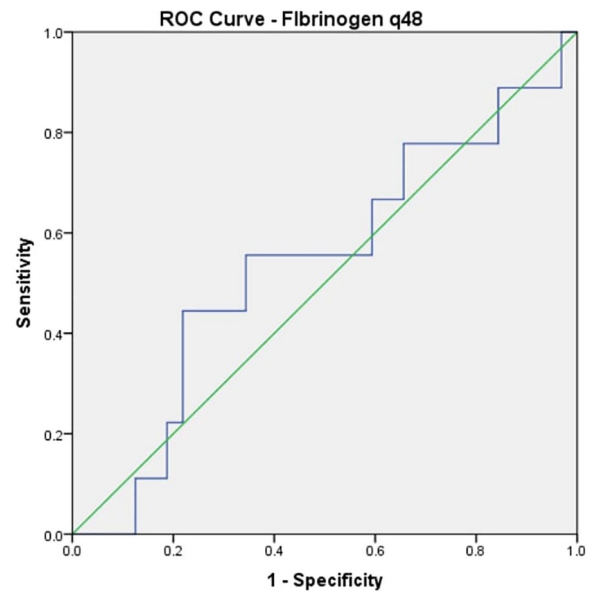Diagonal segments are produced by ties.

Figure 3. ROC curve—Fibrinogen q0h. ROC indicates receiver operating characteristic.

Figure 4. ROC analysis—Fibrinogen q48h. ROC indicates receiver operating characteristic.

Diagonal segments are produced by ties.

Figure 5. ROC analysis—% Change in fibrinogen (delta fibrinogen). ROC indicates receiver operating characteristic.

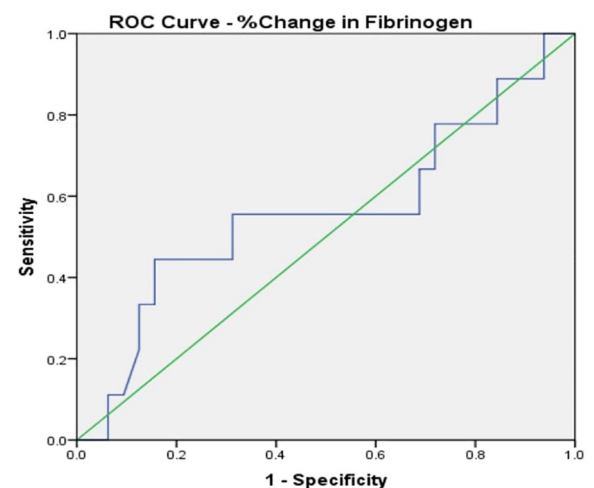contributory factor for clinician ARDS under-recognition[1] but is beyond the scope of this study.

Recommendations and Perspectives

Our study has multiple limitations: (1) sample size calculation was limited by the lack of published data on the prevalence of ARDS in the Philippines, (2) patients who withdrew their consent, (3) the study population was limited to patients with severe pneumonia, (4) the absence of a negative control group, (5) the lack of randomization upon enrollment, (6) the arbitrary decision to recheck fibrinogen levels at 48 hours, (7) the inter-rater variability of adjudication by the clinicians on the diagnosis of ARDS, (8) the single-centered nature of the study, and (9) the lack of data on antibiotic usage, vasopressor use, and lung mechanics. We chose to not record the latter as it was beyond the scope of our research question.

To be able to properly conduct an ARDS study that is contextualized locally, it is imperative to define the local prevalence first. We sense that if such data were present, it would certainly help make future attempts for ARDS biomarkers more accurate. In addition to local ARDS prevalence analysis, an investigation on physician ARDS under-recognition is deemed necessary. If our trial should be replicated, using the same patient cohort, we recommend to include other variables that may predict ARDS development such as the role of clinical scoring, antibiotic usage, lung protective interventions, and lung mechanics monitoring as the analysis of these parameters was not part of our study design. The association of fibrinogen and ARDS patients coming from an indirect or nonpulmonary etiology should also be considered. These patients contribute a significant part of the ARDS population and perhaps fibrinogen could be a possible biomarker for these select patients as well and we recommend a separate trial to include these patients. The optimal timing of fibrinogen

Table 5. Area under the curve analysis.

DISCRIMINANT VARIABLE	AREA UNDER THE CURVE	STD. ERROR	ASYMPTOTIC SIG.	SENSITIVITY, %	SPECIFICITY, %
Fibrinogen, mg/dL, q0h	0.492	0.094	.932[ns]	41.7	57.1
Fibrinogen, mg/dL, q48h	0.538	0.112	.729[ns]	55.6	65.6
% Change in fibrinogen or delta fibrinogen	0.561	0.121	.581[ns]	55.6	62.5

ns—not significant.

determination and redetermination should also be explored. No studies to date have extensively considered the role of fibrinogen with ARDS development. Perhaps, an initial animal study design has a particular role in answering this clinical question. Finally, the role of PEEP regarding fibrinogen levels, as what was observed in this analysis, is still unclear. Current guidelines recommend a low tidal volume and high PEEP strategy to prevent VILI. However, PEEP may also induce lung parenchymal inflammation and may affect levels of fibrinogen and is also an avenue ripe for research.

Conclusions

Based on the results of this study, fibrinogen and delta fibrinogen do not meet the current criteria to serve as a biomarker in predicting progression to ARDS among patients with severe pneumonia.

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Author Contributions

All authors contributed equally in the conceptualization of the study. OU and ML carried out the data collection and transferring to electronic format. OU and ML have equal contributions in terms of drafting and writing the manuscript. JC and EA both proof-read and added vital inputs prior to the finalization of the paper.

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